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Radiolabeling by aluminum fluoride-18 complexation: method optimization on a NODA-based model for application to sensitive biomolecule as PET tracers for oncology

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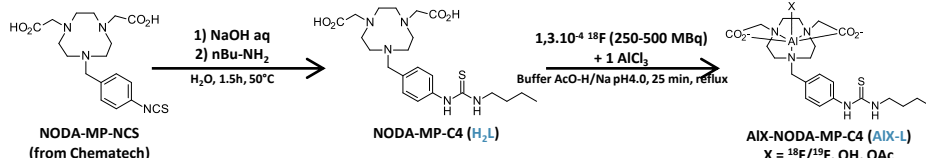
Introduction

Fluorine-18 (¹⁸F) is the most favorable positron emitter for tumor imaging. However, direct ¹⁸F-labeling of biomolecules is challenging as it involves multiple steps and stringent conditions that are generally not suitable for biomolecules whose integrity may be altered. Over the past decade, an elegant new approach has been developed by coordination of aluminum fluoride [Al^{18}F].^(a) The objective of this work was to implement such a method and to find the mildest conditions compatible with heat- or acid-sensitive biomolecules. To evaluate $\{\text{Al}^{18}\text{F}\}$ complexation, NODA-MP-C4, a derivative of the commercially available NODA-MP-NCS, was prepared as a model compound. This model bears a thiourea function to mimic that present in the final conjugates. To guide the operational conditions in radiochemistry, a complementary study in cold series was performed.

Materials and methods

Radiochemistry

1. Production and purification of ¹⁸F
2. Radiolabeling of H₂L
3. Radiofluorination yield determination by radio-HPLC



"Cold" chemistry

1. Synthesis of references
2. Identification of references by LC-MS
3. Optimization of the analytic LC method

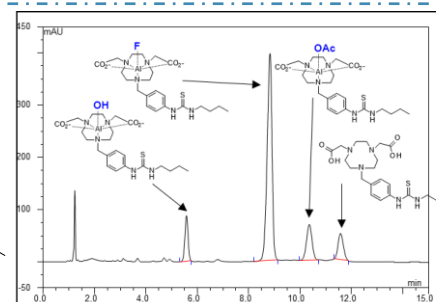
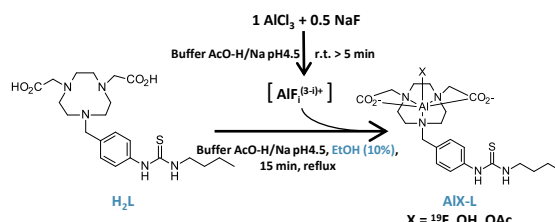


Fig 1: Representative chromatogram of references
Column: Kinetex Evo C18 100 x 4.6mm 5 μm, mobile phase: acetate buffer pH4.5/MeCN 85/15 isocratic, flow rate: 1 mL/min, injection volume: 25 μL, UV detection: 254 nm

Results and discussion

Table: Radiofluorination yield according to ¹⁸F concentration, reactor type and number of pots

N°	¹⁸ F activity (MBq)	¹⁸ F volume (μL)	Reaction volume (μL)	Reactor type	1 or 2 pot(s) ¹	Radiofluorination yield (%)
1	250	50	110	Tube	2	32 %
2	250	50	110	Tube	1	48 %
3	500	50	110	Tube	2	22 %
4	500	50	110	Tube	1	24 %
Fluorine-18 transport tubing replacement						
5	250	50	110	Tube	2	87 %
6	250	50	110	Tube	1	81 %
7	500	50	110	Tube	2	83 %
8	500	50	110	Tube	1	82 %
9	500	50	110	Vial	1	75 %
10	500	25	85	Vial	1	71 %
11	500	25	85	Vial	1	74 %
12	250	12.5	72.5	Vial	1	76 %
13	250	12.5	72.5	Vial	1	79 %

¹tube = test tube = open reactor; vial = for HPLC sample = sealed reactor
²one-pot = mixture of H₂L, AlCl₃ and ¹⁸F; two-pot = premixture of AlCl₃ and ¹⁸F added on H₂L

-Reactor wall thickness influences the inertia to reach the reflux and the real time of warming.
-Transport tubing replacement highlights the impact of fluorine-18 molar activity (ratio ¹⁸F/¹⁹F) on radiofluorination yield

On Kinetex C18 column:

-Radio detection: good separation between uncomplexed $\{\text{Al}^{18}\text{F}\}$ + ¹⁸F- and radiolabelled $\text{Al}^{18}\text{F-L}$

-UV detection: no separation of the different AIX-L species

Change for Kinetex Evo C18 (Fig 1.)

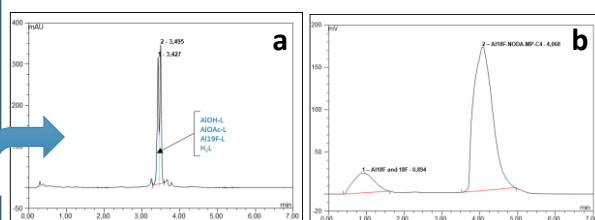


Fig 2: Representative radio-HPLC chromatograms of the radiolabeling reaction mixture (a: UV 254 nm, b: radio)
Column: Kinetex C18 50 x 2.1 mm 2.6 μm, mobile phase: H₂O/MeCN, gradient: 95/5 to 5/95, flow rate: 0.7 mL/min, injection volume: 5 μL

Conclusion

Al^{18}F -NODA-MP-C4 was obtained with a reproducible satisfactory radiofluorination yield (79 % ± 8 % (n=9)) on comparison with reported results on NODA-derivatives (60 % to 90 %).^(b,c)

Bibliographic references:

- (a) McBride, W. J. et al. *J. Nucl. Med.* 2009, 50 (6), 991–998.
(b) Huynh, P. T. et al. *New J. Chem.* 2019, 43 (38), 15389–15395.
(c) Shetty, D. et al. *Bioorg. Med. Chem.* 2012, 20 (19), 5941–5947.

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